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Certificate

The attached documents are exact copies of the international patent application described on the following page, as originally filed.

Attestation

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet international spécifiée à la page suivante.

Den Haag, den
The Hague,
La Haye, le

26 OKT. 2004

Der Präsident des Europäischen Patentamts
Im Auftrag
For the President of the European Patent Office
Le Président de l'Office européen des brevets
p.o.

Y. Marinus-v.d. Nouweland

Patentanmeldung Nr.
Patent application no.
Demande de brevet n°

PCT/EP 03/10746

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: PCT/EP 03/10746

Anmelder:
Applicant(s):
Demandeur(s): 1. ACTELION PHARMACEUTICALS LTD - Allschwil, Switzerland

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Titre de l'invention: Novel Pyridine derivatives

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PCT REQUEST

Actell 51/U7

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V	**Designation of States**		
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT	
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	--	
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	**Exclusion(s) from precautionary designations**	NONE	
VI	**Priority claim**	NONE	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

Actelion 51/U7

NOVEL PYRIDINE DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel 4-(piperidinyl- and pyrrolidinyl-alkyl-ureido)-pyridine derivatives of the General Formula 1 and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of the General Formula 1 and especially their use as neurohormonal antagonists.

BACKGROUND OF THE INVENTION

Urotensin II is a cyclic 11-amino acid peptide neurohormone considered to be the most potent vasoconstrictor known, up to 28-fold more potent than endothelin-1. The effects of urotensin II are mediated through activation of a G-protein coupled receptor, the UT receptor, also known as GPR14 or SENR (Ames RS, et al, "Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14" Nature (1999) 401, 282-6. Mori M, Sugo T, Abe M, Shimomura Y, Kurihara M, Kitada C, Kikuchi K, Shintani Y, Kurokawa T, Onda H, Nishimura O, Fujino M. "Urotensin II is the endogenous ligand of a G-protein-coupled orphan receptor, SENR (GPR14)" Biochem. Biophys. Res. Commun. (1999) 265,123-9. Liu Q, Pong SS, Zeng Z, et al, "Identification of urotensin II as the endogenous ligand for the orphan G-protein-coupled receptor GPR14" Biochem. Biophys. Res. Commun. (1999) 266, 174-178) Urotensin II and its receptor are conserved across evolutionarily distant species, suggesting an important physiological role for the system (Bern HA, Pearson D, Larson BA, Nishioka RS. "Neurohormones from fish tails: the caudal neurosecretory system. I. Urophysiology and the caudal neurosecretory system of fishes" Recent Prog. Horm. Res. (1985) 41, 533-552). In euryhaline fish, urotensin II has an osmoregulatory role, and in mammals urotensin II exerts potent and complex hemodynamic actions. The response to

urotensin II is dependent on the anatomical source and species of the tissue being studied. (Douglas SA, Sulpizio AC, Piercy V, Sarau HM, Ames RS, Aiyar NV, Ohlstein EH, Willette RN. "Differential vasoconstrictor activity of human urotensin-II in vascular tissue isolated from the rat, mouse, dog, pig, marmoset and cynomolgus monkey" Br. J. Pharmacol. (2000) 131, 1262-1274. Douglas, SA, Ashton DJ, Sauermelch CF, Coatney RW, Ohlstein DH, Ruffolo MR, Ohlstein EH, Aiyar NV, Willette R "Human urotensin-II is a potent vasoactive peptide: pharmacological characterization in the rat, mouse, dog and primate" J. Cardiovasc. Pharmacol. (2000) 36, Suppl 1:S163-6).

Like other neurohormones, urotensin II has growth stimulating and profibrotic actions in addition to its vasoactive properties. Urotensin II increases smooth muscle cell proliferation, and stimulates collagen synthesis (Tzandis A, et al, "Urotensin II stimulates collagen synthesis by cardiac fibroblasts and hypertrophic signaling in cardiomyocytes via G(alpha)q- and Ras-dependent pathways" J. Am. Coll. Cardiol. (2001) 37, 164A. Zou Y, Nagai R, and Yamazaki T, "Urotensin II induces hypertrophic responses in cultured cardiomyocytes from neonatal rats" FEBS Lett (2001) 508, 57-60). Urotensin II regulates hormone release (Silvestre RA, et al, "Inhibition of insulin release by urotensin II-a study on the perfused rat pancreas" Horm Metab Res (2001) 33, 379-81). Urotensin II has direct actions on atrial and ventricular myocytes (Russell FD, Molenaar P, and O'Brien DM "Cardiostimulant effects of urotensin-II in human heart in vitro" Br. J. Pharmacol. (2001) 132, 5-9). Urotensin II is produced by cancer cell lines and its receptor is also expressed in these cells. (Takahashi K, et al, "Expression of urotensin II and urotensin II receptor mRNAs in various human tumor cell lines and secretion of urotensin II-like immunoreactivity by SW-13 adrenocortical carcinoma cells" Peptides (2001) 22, 1175-9; Takahashi K, et al, "Expression of urotensin II and its receptor in adrenal tumors and stimulation of proliferation of cultured tumor cells by urotensin II" Peptides (2003) 24, 301-306; Shenouda S, et al, "Localization of urotensin-II immunoreactivity in normal human kidneys and renal carcinoma" J Histochem Cytochem (2002) 50, 885-889). Urotensin II and its receptor are found in spinal cord and brain tissue, and intracerebroventricular infusion of urotensin II into mice induces behavioral changes (Gartlon J, et al, "Central effects of

urotensin-II following ICV administration in rats" Psychopharmacology (Berlin) (2001) 155, 426-33).

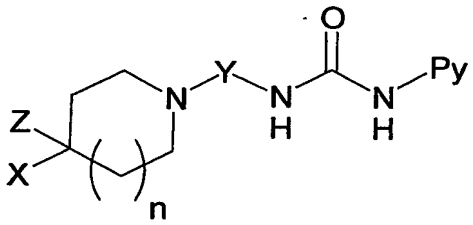
Dysregulation of urotensin II is associated with human disease. Elevated circulating levels of urotensin II are detected in hypertensive patients, in heart failure patients, in diabetic patients, and in patients awaiting kidney transplantation (Totsune K, et al, "Role of urotensin II in patients on dialysis" Lancet (2001) 358, 810-1; Totsune K, et al, "Increased plasma urotensin II levels in patients with diabetes mellitus" Clin Sci (2003) 104, 1-5; Heller J, et al, "Increased urotensin II plasma levels in patients with cirrhosis and portal hypertension" J Hepatol (2002) 37, 767-772).

Substances with the ability to block the actions of urotensin II are expected to prove useful in the treatment of various diseases. WO-2001/45694, WO-2002/78641, WO-2002/78707, WO-2002/79155, WO-2002/79188, WO-2002/89740, WO-2002/89785, WO-2002/89792, WO-2002/89793, WO-2002/90337, WO-2002/90348 and WO-2002/90353 disclose certain sulfonamides as urotensin II receptor antagonists, and their use to treat diseases associated with a urotensin II imbalance. WO-2001/45700 and WO-2001/45711 disclose certain pyrrolidines or piperidines as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. These derivatives are different from the compounds of the present invention as they do not comprise urea derivatives bearing a 4-pyridinyl-like moiety. WO-2002/047456 and WO-2002/47687 disclose certain 2-amino-quinolones as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. WO-2002/058702 discloses certain 2-amino-quinolines as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. WO-2001/66143 discloses certain 2,3-dihydro-1H-pyrrolo[2,3-b]quinolin-4-ylamine derivatives useful as urotensin II receptor antagonists, WO-2002/00606 discloses certain biphenyl compounds useful as urotensin II receptor antagonists, and WO-2002/02530 also discloses certain compounds useful as urotensin II receptor antagonists.

EP 428434 discloses certain alkylureidopyridines as neurokinin and substance P antagonists. WO-99/21835 discloses certain ureidoquinolines as H+-ATPase and bone resorption inhibitors. WO-01/009088 discloses certain substituted heteroarylureas as inhibitors of the CCR-3 receptor. All of these ureidopyridine derivatives differ in their composition from compounds of the present invention. The present invention comprises *N*-(cyclic amino alkyl)-*N'*-pyridin-4-yl urea derivatives which are novel compositions of matter and which are useful as urotensin II receptor antagonists.

DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the General Formula 1.



General Formula 1

wherein:

Py represents pyridin-4-yl which is disubstituted in positions 2 and 6, whereby the substituent in position 2 is lower alkyl, aryl-lower alkyl, or (*E*)-2-aryl-ethen-1-yl, and the substituent in position 6 is hydrogen or lower alkyl;

X represents aryl; aryl-O-; aryl-lower alkyl-; R^1-SO_2NR^2-; R^1-$CONR^2$-; R^1-NR^3CONR^2-; R^1-NR^2CO-; or X and Z represent together with the carbon atom to which they are attached an exocyclic double bond which bears an aryl substituent at the thus formed methylene group;

Y represents -$C(R^4)(R^5)(CH_2)_m$- or -$(CH_2)_mC(R^4)(R^5)$-;

Z represents hydrogen; in case X represents aryl or aryl-lower alkyl Z represents hydrogen, hydroxyl, carboxyl, R^1-NR^2CO-; or in case X represents aryl or aryl-lower alkyl and n represents the number 0, Z represents hydrogen, hydroxyl, carboxyl, R^1-NR^2CO-, aryl, aryl-lower alkyl;

n represents the numbers 0 or 1;

m represents the numbers 1 or 2;

R^1 represents aryl; lower alkyl; aryl-lower alkyl; or a saturated carbocyclic ring;

R^2 and R^3 represent independently hydrogen; lower alkyl; aryl-lower alkyl; or a saturated carbocyclic ring;

R^4 represents hydrogen; lower alkyl; aryl; aryl-lower alkyl; or forms together with R^5 a saturated carbocyclic ring including the carbon atom to which R^4 and R^5 are attached as ring atom;

R^5 represents hydrogen; methyl; or forms together with R^4 a saturated carbocyclic ring including the carbon atom to which R^4 and R^5 are attached as ring atom;

and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates; as well as their pharmaceutically acceptable salts, solvent complexes, and morphological forms.

In the definitions of the General Formula 1 the expression 'aryl' means a substituted or unsubstituted aromatic carbocyclic or heterocyclic ring system, consisting of a five- or six- membered aromatic ring, or of a fused five-six or six-six aromatic ring system. Preferred aryl groups are for example 2-furyl; 2-thienyl; phenyl; 2-methylphenyl; 2-biphenyl; 2-methoxyphenyl; 2-phenoxyphenyl; 2-chlorophenyl; 2-bromophenyl; 2-*i*-propylphenyl; 2-fluorophenyl; 2-methylsulfonylphenyl; 2-cyanophenyl; 2-trifluoromethylphenyl; 3-methylphenyl; 3-biphenyl; 3-phenoxyphenyl; 3-methoxyphenyl; 3-chlorophenyl; 3-bromophenyl; 3-fluorophenyl; 3-cyanophenyl; 3-trifluoromethylphenyl; 3-carboxyphenyl; 4-methylphenyl; 4-ethylphenyl; 4-*i*-propylphenyl; 4-phenyloxyphenyl; 4-trifluoromethylphenyl; 4-trifluoromethoxyphenyl; 4-phenoxyphenyl; 4-cyanophenyl; 4-hydroxyphenyl; 4-acetylaminophenyl; 4-methanesulfonylphenyl; 4-*n*-propylphenyl; 4-*iso*-propylphenyl; 4-*tert*-butylphenyl; 4-*n*-pentylphenyl; 4-biphenyl; 4-chlorophenyl; 4-bromophenyl; 4-bromo-2-ethylphenyl; 4-fluorophenyl; 2,4-difluorophenyl; 4-*n*-butoxyphenyl; 2,6-dimethoxyphenyl; 3,5-bis-

trifluoromethylphenyl; 2-pyridyl; 3-pyridyl; 4-pyridyl; 1-naphthyl; 2-naphthyl; 4-(pyrrol-1-yl)phenyl; 4-benzoylphenyl; 5-dimethylaminonaphth-1-yl; 5-chloro-3-methylthiophen-2-yl; 5-chloro-3-methyl-benzo[b]thiophen-2-yl; 3-(phenylsulfonyl)-thiophen-2-yl; 2-(2,2,2-trifluoroacetyl)-1-2,3,4-tetrahydroisoquinolin-7-yl; 4-(3-chloro-2-cyanophenyloxy)phenyl; 2-(5-benzamidomethyl)thiophenyl; 4,5-dichlorothien-2-yl; 5-quinolyl-; 6-quinolyl; 7-quinolyl; 8-quinolyl; (2-acetylamino-4-methyl)thiazol-5-yl; or 1-methylimidazol-4-yl.

In the definitions of the General Formula 1 the expression 'lower alkyl' means straight or branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms. Preferred examples of lower alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, and n-heptyl.

In the definitions of the General Formula 1 the expression 'saturated carboxyclic ring' means a saturated cyclic alkyl group with three to six carbon atoms. Preferred examples of saturated carbocyclic rings are cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

In the definitions of the General Formula 1 the expression 'aryl-lower alkyl' means a lower alkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Preferred examples of aryl-lower alkyl groups are 3-phenylpropyl, phenethyl, benzyl and benzyl substituted in the phenyl ring with hydroxy, lower alkyl, lower alkyloxy, or halogen.

Preferred examples of '(*E*)-2-aryl-ethen-1-yl' groups are (*E*)-2-phenylethen-1-yl, (*E*)-2-(4-fluorophenyl)ethen-1-yl and (*E*)-3-phenylpropen-1-yl.

The present invention encompasses pharmaceutically acceptable salts of compounds of the General Formula 1. This encompasses either salts with inorganic acids or organic acids like hydrohalogenic acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, malic acid, methylsulfonic acid, p-tolylsulfonic acid and the like or in case the compound of formula 1 is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium,

potassium, or calcium salts, etc. The compounds of General Formula 1 can also be present in form of zwitterions.

The present invention encompasses different solvation complexes of compounds of General Formula 1. The solvation can be effected in the course of the manufacturing process or can take place separately, e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of General Formula 1.

The present invention further encompasses different morphological forms, e.g. crystalline forms, of compounds of General Formula 1 and their salts and solvation complexes. Particular heteromorphs may exhibit different dissolution properties, stability profiles, and the like, and are all included in the scope of the present invention.

The compounds of the General Formula 1 might have one or more asymmetric carbon atoms and may be prepared in form of configurational isomers, optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates. The present invention encompasses all these forms. They are prepared by stereoselective synthesis, or by separation of mixtures in a manner known per se, i.e. by column chromatography, thin layer chromatography, HPLC, crystallization, etc.

Preferred compounds of General Formula 1 are the compounds wherein m represents 1 and Py, R^4, R^5, X, Z, and n have the meaning given in General Formula 1 above.

Another group of preferred compounds of General Formula 1 consists of those compounds wherein Py represents pyridin-4-yl disubstituted in position 2 and 6 with lower-alkyl, and X, Y, Z, and n have the meaning given in General Formula 1 above.

Another group of preferred compounds of General Formula 1 consists of those compounds wherein Py represents pyridin-4-yl disubstituted in position 2 with aryl-lower alkyl and in position 6 with lower-alkyl, and X, Y, Z, and n have the meaning given in General Formula 1 above.

Another group of preferred compounds of General Formula 1 consists of those compounds wherein R^4 and R^5 represent independently hydrogen or methyl, and Py, X, Z, n, and m have the meaning given in General Formula 1 above.

Another group of preferred compounds of General Formula 1 consists of those compounds wherein X represents aryl or aryl-lower alkyl, Z represents HO-, n represents 1, and Py, and Y have the meaning given in General Formula 1 above.

Another group of preferred compounds of General Formula 1 consists of those compounds wherein X represents aryl or aryl-lower alkyl, Z represents hydrogen, n represents 1, and Py, and Y have the meaning given in General Formula 1 above.

Another group of preferred compounds of General Formula 1 consists of those compounds wherein X and Z independently represent aryl, n represents 0, and Py, and Y have the meaning given in General Formula 1 above.

Another group of preferred compounds of General Formula 1 consists of those compounds wherein X represents R^1-SO_2NR^2-, R^1-$CONR^2$-, R^1-NR^2CONR^3-; Z represents hydrogen, and R^1, R^2, R^3, Py, and Y have the meaning given in General Formula 1 above.

Another group of preferred compounds of General Formula 1 consists of those compounds wherein X represents R^1-NR^2CO-; Z represents aryl or hydrogen, and R^1, R^2, Py, and Y have the meaning given in General Formula 1 above.

A group of especially preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, Py represents pyridin-4-yl disubstituted in position 2 and 6 with lower-alkyl, and X, R^4, R^5, Z, and n have the meaning given in General Formula 1 above.

Another group of especially preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, Py represents pyridin-4-yl disubstituted in position 2 with aryl-lower alkyl and in position 6 with lower-alkyl, and X, R^4, R^5, Z, and n have the meaning given in General Formula 1 above.

Another group of especially preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, R^4 and R^5 represent hydrogen, and Py, X, Z, and n have the meaning given in General Formula 1 above.

Another group of especially preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, X represents aryl or aryl-lower alkyl, Z represents HO-, n represents 1, and Py, R^4, and R^5 have the meaning given in General Formula 1 above.

Another group of especially preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, X represents aryl or aryl-lower alkyl, Z represents hydrogen, n represents 1, and Py, R^4, and R^5 have the meaning given in General Formula 1 above.

Another group of especially preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, X represents R^1-SO_2NR^2-, R^1-$CONR^2$-, R^1-NR^2CONR^3-; Z represents hydrogen, and n, Py, R^1, R^2, R^3, R^4, and R^5 have the meaning given in General Formula 1 above.

Another group of especially preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, X represents R^1-NR^2CO-; Z represents aryl or hydrogen, n represents 1, and Py, R^1, R^2, R^4, and R^5 have the meaning given in General Formula 1 above.

A group of most preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, R^4 and R^5 represent hydrogen, Py represents pyridin-4-yl disubstituted in position 2 with methyl and in position 6 with lower-alkyl, and X, Z, and n have the meaning given in General Formula 1 above.

Another group of most preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, R^4 and R^5 represent hydrogen, X represents aryl or aryl-lower alkyl, Z represents HO-, n represents 1, and Py has the meaning given in General Formula 1 above.

Another group of most preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, R^4 and R^5 represent hydrogen, X

represents aryl or aryl-lower alkyl, Z represents hydrogen, n represents 1, and Py has the meaning given in General Formula 1 above.

Another group of most preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, R^4 and R^5 represent hydrogen, X represents aryl-SO_2NR^2-, Z represents hydrogen, and R^2, n and Py have the meaning given in General Formula 1 above.

Another group of most preferred compounds of General Formula 1 consists of those compounds wherein m represents 1, R^4 and R^5 represent hydrogen, X represents aryl-NR^2CO- or aryl-lower alkyl-NR^2CO-, Z represents aryl or hydrogen, n represents 1, and Py and R^2 have the meaning given in General Formula 1 above.

Examples of particularly preferred compounds of General Formula 1 are selected from the group consisting of:

N-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-benzenesulfonamide;

N-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-fluoro-benzenesulfonamide;

N-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-*N*-propyl-benzenesulfonamide;

N-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-*N*-propyl-benzenesulfonamide;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea;

1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide;

1-(2,6-Dimethyl-pyridin-4-yl)-3-[2-(3,3-diphenyl-pyrrolidin-1-yl)-ethyl]-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea;

N-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-benzenesulfonamide;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-ethyl-6-methyl-pyridin-4-yl)-urea;

1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide;

N-Ethyl-4-methoxy-*N*-(1-{2-[3-(2-methyl-6-propyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-6-propyl-pyridin-4-yl)-urea;

1-{2-[3-(2-Methyl-6-propyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide;

N-Ethyl-4-methoxy-*N*-(1-{2-[3-(2-methyl-6-phenethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide;

1-(2-{3-[2-Methyl-6-((*E*)-styryl)-pyridin-4-yl]-ureido}-ethyl)-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-fluoro-phenyl)-vinyl]-6-methyl-pyridin-4-yl}-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-((*E*)-styryl)-pyridin-4-yl]-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-fluoro-phenyl)-vinyl]-pyridin-4-yl}-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-chloro-phenyl)-vinyl]-pyridin-4-yl}-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-phenethyl-pyridin-4-yl)-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[2-(4-fluoro-phenyl)-ethyl]-pyridin-4-yl}-urea;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-{2-[2-(4-fluoro-phenyl)-ethyl]-6-methyl-pyridin-4-yl}-urea;

1-{2-[3-(2-Methyl-6-phenethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-pyridin-4-yl)-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-benzyl-pyridin-4-yl)-urea.

Because of their ability to inhibit the actions of urotensin II, the described compounds can be used for treatment of diseases which are associated with an increase in vasoconstriction, proliferation or other disease states associated with the actions of urotensin II. Examples of such diseases are hypertension, atherosclerosis, angina or myocardial ischemia, congestive heart failure, cardiac insufficiency, cardiac arrhythmias, renal ischemia, chronic kidney disease, renal failure, stroke, cerebral vasospasm, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, diabetes, diabetic arteriopathy, diabetic nephropathy, connective tissue diseases, cirrhosis, asthma, chronic obstructive pulmonary disease, high-altitude pulmonary edema, Raynaud's syndrome, portal hypertension, thyroid dysfunction, pulmonary edema, pulmonary hypertension, or pulmonary fibrosis. They can also be used for prevention of restenosis after balloon or stent angioplasty, for the treatment of cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, sickle cell acute chest syndrome, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, addictions, schizophrenia, Alzheimer's disease, anxiety, obsessive-compulsive behavior, epileptic seizures, stress, depression, dementias, neuromuscular disorders, neurodegenerative diseases, as well as other diseases related to a dysregulation of urotensin II or urotensin II receptors.

These compositions may be administered in enteral or oral form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form like

sprays and aerosols, or rectally in form of suppositories. These compounds may also be administered in intramuscular, parenteral or intravenous form, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of formula 1 as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients, which are usual in the pharmaceutical industry, like lactose, maize or derivatives thereof, talcum, stearic acid or salts of these materials.

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols etc. may be used. For the preparation of solutions and sirups e.g. water, polyols, saccharose, glucose etc. are used. Injectables are prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin, liposomes etc. Suppositories are prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols etc.

The compositions may contain in addition preservatives, stabilisation improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, anti-oxidants etc.

The compounds of General Formula 1 may also be used in combination with one or more other therapeutically useful substances e.g. α- and β-blockers like phentolamine, phenoxybenzamine, atenolol, propranolol, timolol, metoprolol, carteolol, carvedilol, etc.; with vasodilators like hydralazine, minoxidil, diazoxide, flosequinan, etc.; with calcium-antagonists like diltiazem, nicardipine, nimodipine, verapamil, nifedipine, etc.; with angiotensin converting enzyme-inhibitors like cilazapril, captopril, enalapril, lisinopril etc.; with potassium channel activators like pinacidil, chromakalim, etc.; with angiotensin receptor antagonists like losartan, valsartan, candesartan, irbesartan, eprosartan, telmisartan, and tasosartan, etc.; with diuretics like hydrochlorothiazide, chlorothiazide, acetolamide, bumetanide, furosemide, metolazone, chlortalidone, etc.; with sympatholytics like methyldopa, clonidine, guanabenz, reserpine, etc.; with endothelin receptor antagonists like bosentan, tezosentan, darusentan, atrasentan, enrasentan, or sitaxsentan, etc.;

with anti-hyperlipidemic agents like lovastatin, pravistatin, fluvastatin, atorvastatin, cerivastatin, simvastatin, etc.; and other therapeutics which serve to treat high blood pressure, vascular disease or other disorders listed above.

The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given daily in oral form should be between about 3 mg and about 3 g, preferably between about 5 mg and about 1 g, especially preferred between 10 mg and 300 mg, per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses of equal weight per day. As usual children should receive lower doses which are adapted to body weight and age.

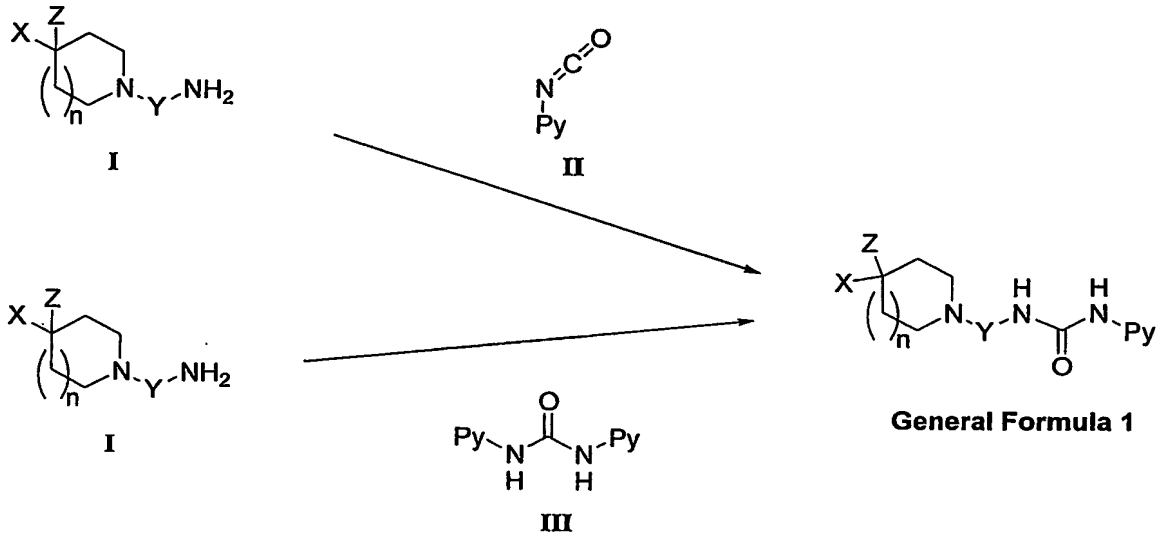
GENERAL PREPARATION OF COMPOUNDS OF THE INVENTION

Compounds of the General Formula 1 can be prepared using methods generally known in the art, according to the general sequence of reactions outlined below. For simplicity and clarity reasons sometimes only a few of the possible synthetic routes that lead to compounds of General Formula 1 are described.

For the synthesis of compounds of General Formula 1 general synthetic routes illustrated in Schemes A through G can be employed. The generic groups Py, R^1, R^2, R^3, R^4, R^5, X, Y, Z, n, and m employed in Schemes A through G have the definitions given in General Formula 1 above. Other abbreviations used are defined in the Experimental Section. Some instances of the generic groups X and Z might be incompatible with the assembly illustrated in Schemes A through G and so will require the use of protecting groups (PG). The use of protecting groups is well known in the art (see for example "Protective Groups in Organic Synthesis", T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999). For the purposes of this discussion, it will be assumed that such protecting groups as are necessary are in place.

Preparation of compounds of General Formula 1. These compounds are prepared according to Scheme A.

Scheme A

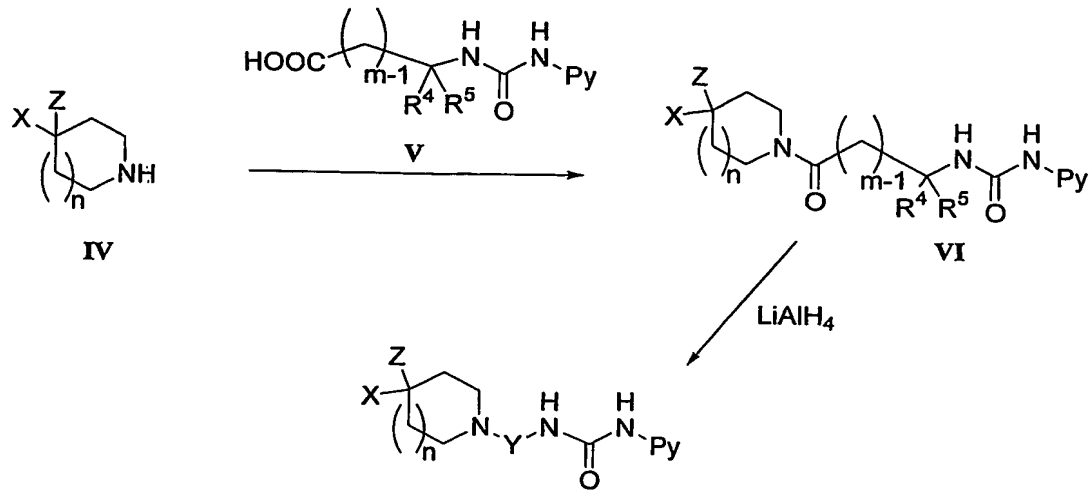


Achiral, racemic or enantiomerically pure amines of general structure I are reacted with isocyanates of general structure II to provide compounds of General Formula 1. Alternatively, amines of general structure I are reacted with ureas of general structure III to provide compounds of General Formula 1. The preparation of isocyanates of general structure II and of ureas of general structure III is described in Scheme E below. The preparation of amines of general structure I is described in Scheme G below.

Preparation of compounds of General Formula 1 wherein Y is -$(CH_2)_mC(R^4)(R^5)$-.

Compounds of General Formula 1 wherein Y is -$(CH_2)_mC(R^4)(R^5)$- are prepared according to Scheme B.

Scheme B



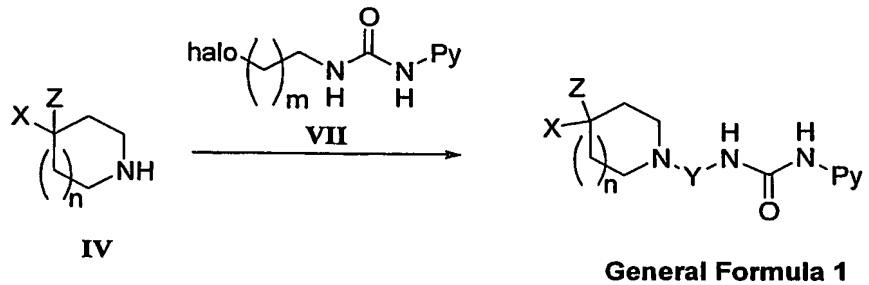
General Formula 1

wherein Y = -$(CH_2)_m$-$C(R^4)(R^5)$-

Achiral, racemic or optically active 4-substituted-piperidines and 3-substituted-pyrrolidines of general structure IV in Scheme B are either commercially available or prepared by methods well known in the art. Ureido acetic- and propionic acid derivatives of general structure V in Scheme B are prepared according to Scheme F below. *N*-Acylation of piperidines and pyrrolidines of general structure IV with ureido acetic- and propionic acid derivatives of general structure V is accomplished in a polar solvent such as DMF in the presence of a small stoichiometric excess of a coupling reagent such as a EDC to provide amides of general structure VI. Selective reduction of the amide carbonyl group with a reagent such as $LiAlH_4$ in a aprotic solvent such as THF provides the target compounds of General Formula 1 wherein Y is -$(CH_2)_mC(R^4)(R^5)$-.

Compounds of General Formula 1 wherein R^4 and R^5 are H. These compounds are alternatively prepared according to the method illustrated in Scheme C.

Scheme C



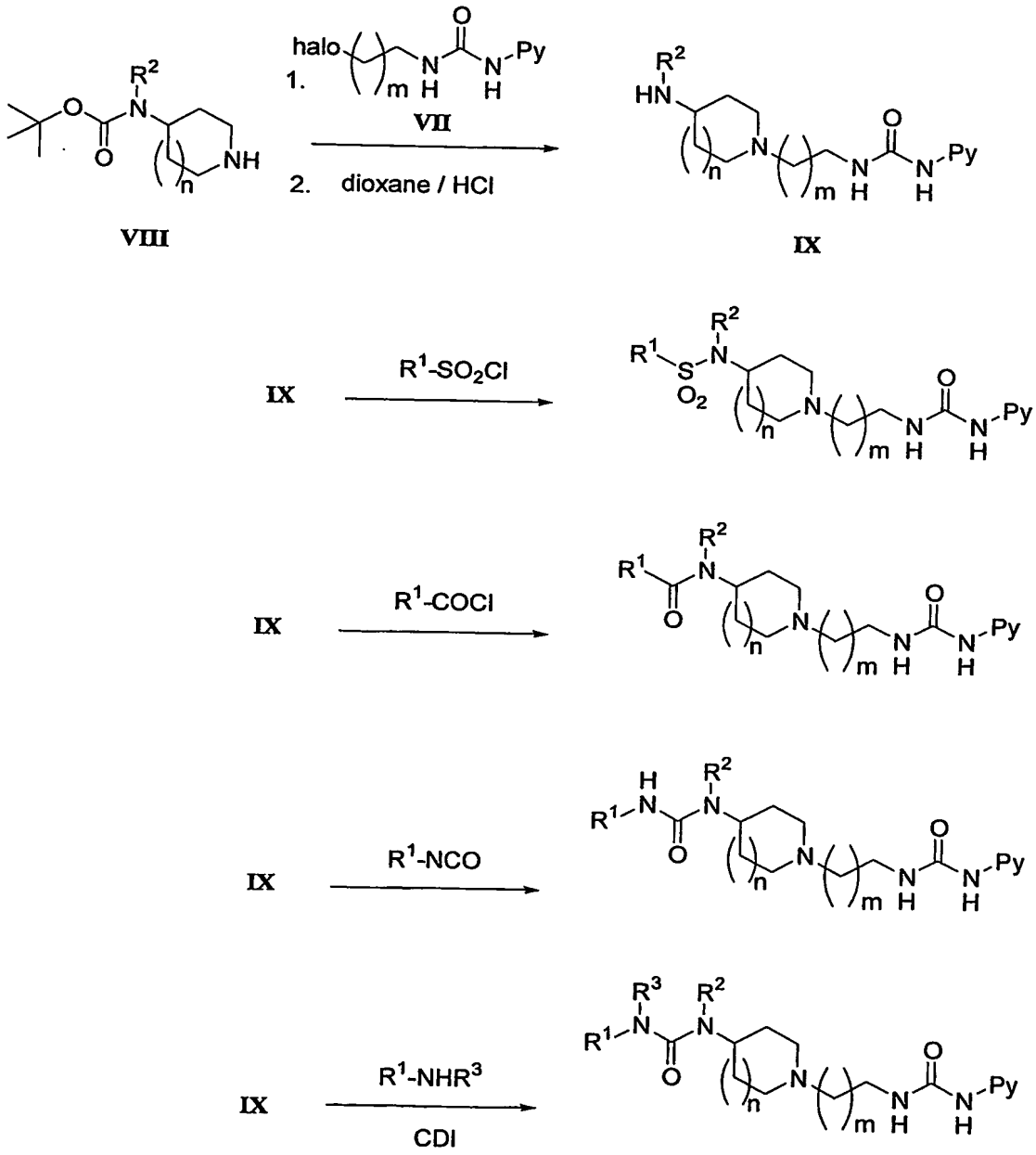
General Formula 1

wherein R^4 and R^5 = H

Achiral, racemic or optically active 4-substituted-piperidines and 3-substituted-pyrrolidines of general structure IV in Scheme C are either commercially available or prepared by methods well known in the art. Haloalkyl ureas of general structure VII in Scheme C are prepared according to Scheme E below. *N*-Alkylation of piperidines and pyrrolidines of general structure IV with haloalkyl ureas of general structure VII is accomplished in a polar solvent such as tetrahydrofuran in the presence of a sub-stoichiometric amount of an iodide salt such as NaI and a small stoichiometric excess of acid scavenger such as $NaHCO_3$ to provide the target compounds of General Formula 1.

Compounds of General Formula 1 wherein X represents R^1-SO_2NR^2-, R^1-$CONR^2$- or R^1-NR^2CONR^3- and Z, R^4 and R^5 represent H. These compounds are alternatively prepared according to the method illustrated in Scheme D.

Scheme D

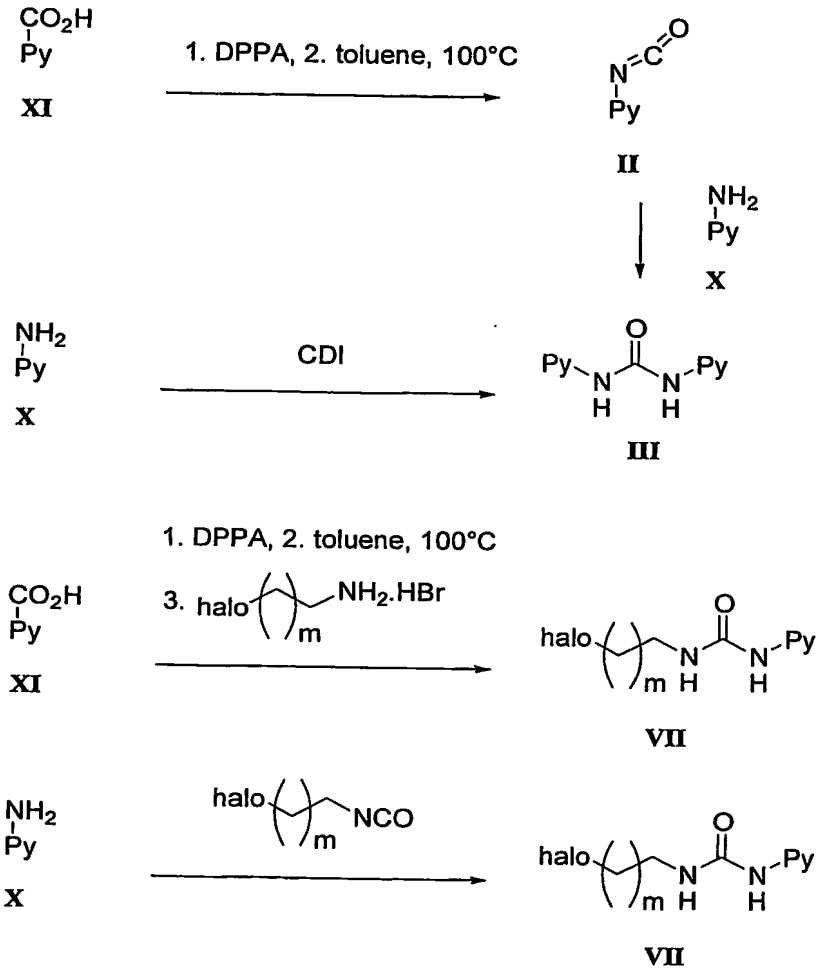


Achiral, racemic or optically active carbamates of general structure VIII are either commercially available or readily prepared by methods well known in the art. Haloalkyl ureas of general structure VII are prepared according to Scheme E

below. Carbamates of general structure VIII are reacted with haloalkyl ureas of general structure VII in a polar solvent such as tetrahydrofuran in the presence of a substoichiometric amount of an iodide salt such as NaI and a small stoichiometric excess of an acid scavenger such as $NaHCO_3$, followed by removal of the carbamate group under acidic conditions, such as reaction with HCl in dioxane or TFA in CH_2Cl_2. The resulting compounds of general structure IX are converted to compounds of General Formula 1 wherein X represents R^1-SO_2NR^2-, R^1-$CONR^2$- or R^1-NR^2CONR^3- and Z, R^4 and R^5 represent H, by reaction with commercially available or well known sulfonylchlorides, isocyanates, or acid chlorides. Compounds of General Formula 1 wherein X represents R^1-NR^3CONR^2-, R^3 represents lower alkyl or aryl-lower alkyl, and Z, R^4 and R^5 represent H, are prepared by reaction of compounds of general structure IX with secondary amines that are commercially available or prepared by methods well known in the art in the presence of a stoichiometric amount of a coupling reagent such as carbonyldiimidazole (CDI).

Synthetic intermediates used in Schemes A, B, C, and D. Synthetic intermediates containing the group Py, as defined in the General Formula 1 above, are obtained by the methods illustrated in Schemes E and F.

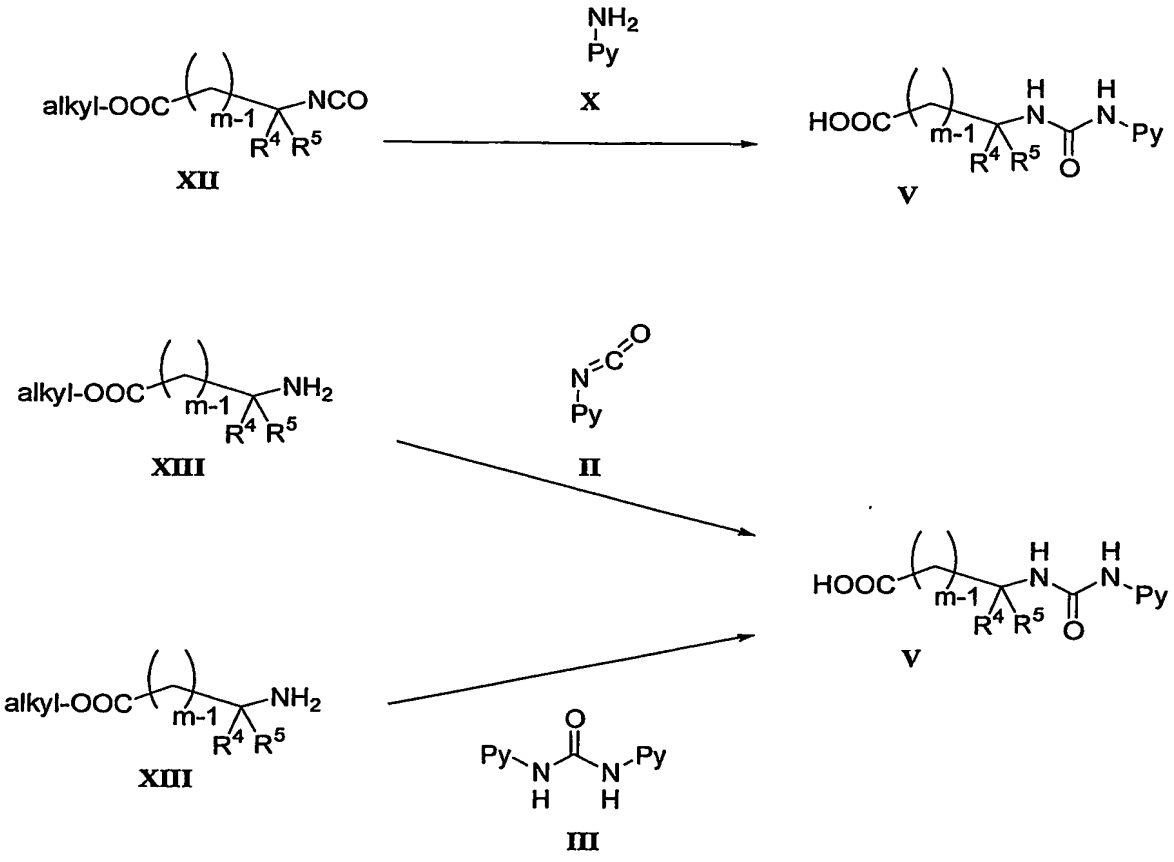
Scheme E



Carboxylic acids of general structure XI are commercially available or are prepared by well known methods. Reaction with diphenylphosphorylazide provides the acyl azide, which undergoes Curtius rearrangement to provide the isocyanates of general structure II, which are used in situ. 4-Aminopyridines of general structure X are commercially available or prepared by methods well known in the art (see for example "A Convenient Preparation of 4-Pyridinamine Derivatives, M. Malinowski, L.Kaczmarek, J. Prakt. Chem. (1988) 330, 154-158). Reaction of 4-aminopyridines of general structure X with isocyanates of general structure II

provides ureas of general structure III. Alternatively, ureas of general structure III are prepared by reaction of 4-aminopyridines of general structure X and a coupling reagent such as CDI in a aprotic solvent such as THF at reflux. Isocyanates of general structure II, reacted with halopropylamine hydrochloride or haloethylamine hydrochloride in the presence of an acid scavenger such as DIPEA, provide ureas of general structure VII. Alternatively, reaction of 4-aminopyridines of general structure X with chloroethylisocyanate or chloropropylisocyanate in a polar aprotic solvent such as tetrahydrofuran provides the ureas of general structure VII.

Scheme F

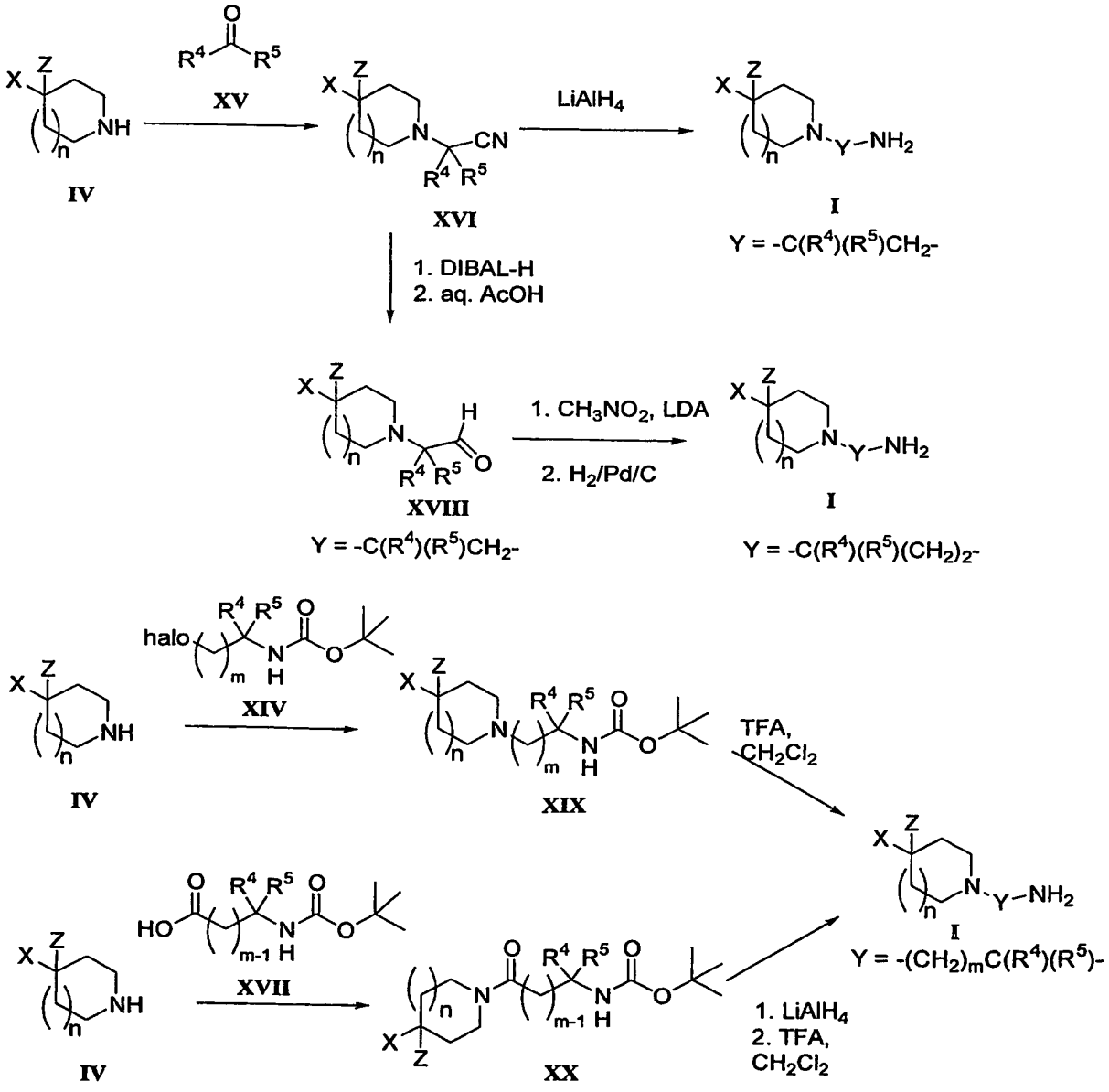


2- or 3-Isocyanato-carboxylic acid esters of General Formula XII are commercially available or prepared by methods well known in the art. Amino acid esters of general structure XIII are commercially available or prepared by methods well known in the art. Reaction of amines of general structure X with 2- or 3-isocyanato-carboxylic acid esters of General Formula XII in a polar aprotic solvent

such as tetrahydrofuran, followed by hydrolysis of the ester in aqueous acid such as HCl, provides carboxylic acids of general structure V. Alternatively, isocyanates of general structure II and ureas of general structure III react with amino acid esters of general structure XIII to provide, after hydrolysis of the ester in aqueous acid such as HCl, carboxylic acids of general structure V.

Synthetic intermediates of general structure IV are obtained by the methods illustrated in Scheme G.

Scheme G



Achiral, racemic or optically active 4-substituted-piperidines and 3-substituted-pyrrolidines of general structure IV in Scheme G are either commercially available or prepared by methods well known in the art. Ketones and aldehydes of General Formula XV are commercially available or are prepared by methods well-known in the art. Reaction of ketones and aldehydes of General Formula XV with 4-substituted-piperidines and 3-substituted-pyrrolidines of general structure IV in presence of a cyanide ion donor such as acetone cyanohydrine provides piperidine and pyrrolidine derivatives of general structure XVI. Alternatively, in case R^4 and R^5 represent H, compounds of general structure XVI are obtained by alkylation of compounds of general structure IV with commercially available haloacetonitrile or 3-halopropionitrile in presence of a small stoichiometric excess of acid scavenger such as DIPEA. Complete reduction of the cyano group with a reducing reagent such as $LiAlH_4$ in a polar aprotic solvent such as THF provides the intermediate primary amines of general structure I, wherein Y is $-C(R^4)(R^5)-CH_2-$. Partial reduction of the cyano group of compounds of general structure XVI with a reducing reagent such as DIBAL-H, followed by aqueous hydrolysis provides aldehydes of general structure XVIII. Condensation with the nitromethane anion and subsequent reduction, for example by catalytic hydrogenation, provides the intermediate primary amines of general structure II, wherein Y is $-C(R^4)(R^5)(CH_2)_2-$. Haloalkyl carbamates of general structure XIV in Scheme G are commercially available or are prepared by methods well-known in the art. *N*-Alkylation of piperidines and pyrrolidines of general structure IV with haloalkyl carbamates of general structure XIV is accomplished in a polar solvent such as THF in the presence of a small stoichiometric excess of acid scavenger such as DIPEA to provide compounds of general structure XIX. Cleavage of the resulting carbamate with methods well known in the art, for example with TFA in a solvent such as CH_2Cl_2, provides the intermediate primary amine derivatives of general structure I wherein Y is $-(CH_2)_mC(R^4)(R^5)-$. Protected amino acids of general structure XVII are commercially available or are prepared by methods well-known in the art. *N*-Acylation of piperidines and pyrrolidines of general structure IV with compounds of general structure XVII is accomplished under well-known conditions, for example in a polar solvent such as DMF in the presence of a small stoichiometric excess of a coupling agent such as a carbodiimide, to provide

compounds of general structure XX. Reduction with a reagent such as $LiAlH_4$ and deprotection provides intermediate primary amines of general structure I wherein Y is $-(CH_2)_mC(R^4)(R^5)-$.

The foregoing general description of the invention will now be further illustrated with a number of non-limiting examples.

EXAMPLES OF THE INVENTION

LIST OF ABBREVIATIONS:

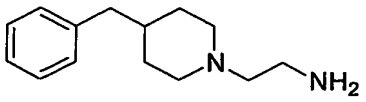
AcOH	acetic acid
aq.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
BSA	bovine serum albumin
cat.	catalytic
CDI	carbonyldiimidazole
DIBAL-H	diisobutylaluminiumhydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphorylazide
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethyl-carbodiimide
EDTA	ethylenediamine tetra-acetic acid
EtOAc	ethyl acetate
Et_2O	diethyl ether
FC	flash chromatography
$Fe(acac)_3$	iron(III)-acetylacetonate
Hex	hexane

HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HV	high vacuum conditions
LC-MS	liquid chromatography-mass spectroscopy
$LiAlH_4$	lithium aluminum hydride
MeOH	methanol
min	minutes
MHz	megahertz
MPLC	medium pressure liquid chromatography
$NaBHAc_3$	sodium triacetoxyborohydride
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
ppm	part per million
PBS	phosphate-buffered saline
$Pd(dppf)Cl_2$	1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex
PG	protecting group
r.t.	room temperature
sat.	saturated
SiO_2	silica gel
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
t_R	retention time

Reactions are routinely performed under an inert atmosphere such as N_2 gas in air dried glassware. Solvents are used as received from the vendor. Evaporations are performed in a rotary evaporator at reduced pressure and a water bath temperature of 50 °C. LC-MS characterizations are performed on a Finnigan HP1100 platform using ESI ionization mode, and positive ion detection with a Navigator AQA detector. Analytical liquid chromatographic separations are performed on a C18 column of 4.6 x 30 mm dimensions and a mobile phase consisting of a 6 minute gradient of 2 – 95% CH_3CN in water containing 0.5% formic acid at a flow rate of 0.45 mL/min. Retention time (t_R) is given in min. TLC is performed on pre-coated silica gel 60 F_{254} glass-backed plates (Merck). MPLC is performed on a Labomatic platform using either normal phase SiO_2-columns and a mobile phase consisting of heptane-EtOAc, or reversed phase C18 columns and a mobile phase consisting of water-MeOH. Preparative HPLC is performed on a Varian/Gilson platform using a C18 column of 21 x 60 mm dimensions and a mobile phase consisting of a gradient of 2 - 95% CH_3CN in water containing 0.5% formic acid.

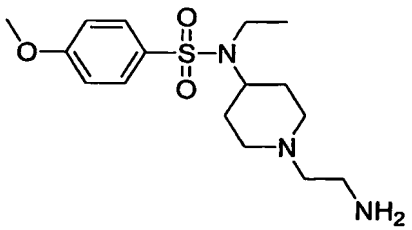
Preparation of Intermediates. Example A.

A1. 2-(4-Benzylpiperidino)-1-ethanamine.



The material is commercially available.

A2. *N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-*N*-ethyl-4-methoxy-benzenesulfonamide.



A2.1. 4-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester.

A mixture of commercially available 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (5.58 g, 28 mmol) and ethylamine (2 M in THF, 50 mL, 100 mmol) in THF (100 mL) is stirred at r.t. for 2 h. $NaBHAc_3$ (8.9 g, 42 mmol) is added and the mixture is stirred for 15 h. The mixture is quenched with 1 M aq. NaOH (100 mL) and stirred at r.t. for 6 h. The mixture is extracted with CH_2Cl_2 (150 mL, then 4 x 50 mL) and the combined organic extracts are washed with 1 M aq. NaOH (30 mL). The organic phase is dried (Na_2SO_4), filtered and evaporated. The residue is dissolved in CH_2Cl_2 (100 mL) and TEA (3 g, 30 mmol) and, subsequently, a solution of 4-methoxy-benzenesulfonylchloride (6.38 g, 30.9 mmol) in CH_2Cl_2 (10 mL) are added at 0°C. The mixture is warmed to r.t. during 15 h and quenched with 1 M aq. NaOH (30 mL). The phases are separated and the organic phase is washed with 1 M aq. NaOH (30 mL), 1 M aq. $KHSO_4$ (2 x 30 mL) and sat. aq. NaCl (30 mL). The organic phase is dried (Na_2SO_4), filtered and evaporated. The residue is purified by FC (SiO_2, EtOAc-heptane) to provide the title compound.

A2.2. *N*-Ethyl-4-methoxy-*N*-piperidin-4-yl-benzenesulfonamide.

A solution of 4-[ethyl-(4-methoxy-benzenesulfonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (11.1 g, 28 mmol) in CH_2Cl_2 (50 mL) is cooled at 0°C and TFA (40 mL) is added. The mixture is stirred at 0°C for 0.5 h and then evaporated. The residue is dissolved in CH_2Cl_2 (50 mL) and 1 M aq. NaOH (50 mL) is added. The mixture is stirred for 15 h at r.t., then the phases are separated and the aq. phase is extracted with CH_2Cl_2 (4 x 30 mL). The combined org. phases are washed with 1 M aq. NaOH (2 x 30 mL), dried (Na_2SO_4), filtered and evaporated to provide the title compound.

A2.3. (2-Bromo-ethyl)-carbamic acid tert-butyl ester.

To 1 N aq. NaOH (200 mL) is added MeOH (400 mL) and the resulting solution is cooled at 20 °C. 2-Bromoethylamine hydrobromide (25.0 g, 122 mmol) is added in a single portion, followed by di-tert-butyl dicarbonate (26.6 g, 122 mmol). The reaction mixture is stirred for 2.5 h. The MeOH is removed on a rotary evaporator,

and the aq. suspension is extracted with CH_2Cl_2 (2 x 175 mL). The combined organic extracts are extracted with 5% aq. citric acid (300 mL), dried ($MgSO_4$), filtered, and evaporated to provide the title compound.

A2.4. (2-{4-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-piperidin-1-yl}-ethyl)-carbamic acid tert-butyl ester.

A mixture of *N*-ethyl-4-methoxy-*N*-piperidin-4-yl-benzenesulfonamide (1.19 g, 4 mmol), 2-bromo-ethyl)-carbamic acid tert-butyl ester (1.12 g, 5.0 mmol) and DIPEA (650 mg, 5 mmol) in THF (30 mL) is heated at reflux for 15 h. The solution is poured into Et_2O (150 mL) and extracted with sat. aq. Na_2CO_3 (2 x 50 mL) and sat. aq. NaCl (30 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by reversed phase MPLC to provide the title compound.

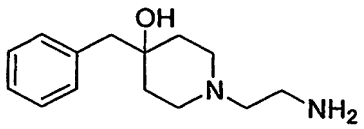
A2.5. *N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-*N*-ethyl-4-methoxy-benzenesulfonamide.

The title compound is prepared from (2-{4-[ethyl-(4-methoxy-benzenesulfonyl)-amino]-piperidin-1-yl}-ethyl)-carbamic acid tert-butyl ester using the method described in Example A2.2.

The following compounds are prepared from 4-oxo-piperidine-1-carboxylic acid tert-butyl ester, ethyl- or n-propylamine, and commercially available arylsulfonylchlorides using the method described in Example A2.

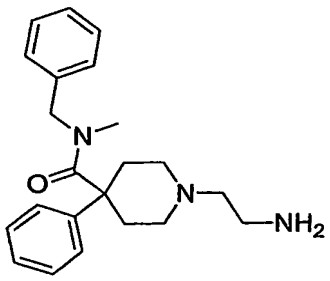
Example No	Example
A3.	*N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-4-methoxy-*N*-propyl-benzenesulfonamide
A4.	*N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-4-fluoro-*N*-propyl-benzenesulfonamide
A5.	*N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-*N*-ethyl-4-fluoro-benzenesulfonamide

A6. 1-(2-Amino-ethyl)-4-benzyl-piperidin-4-ol.



The title compound is prepared from commercially available 4-benzyl-piperidin-4-ol and (2-bromo-ethyl)-carbamic acid tert-butyl ester (Example A2.3) using the methods for the preparation of Example A2.4 and Example A2.5.

A7. 1-(2-Amino-ethyl)-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide.



A7.1. 4-Phenyl-piperidine-1,4-dicarboxylic acid monobenzyl ester.

A suspension of commercially available 4-phenyl-4-carboxypiperidine toluenesulfonate (7.55 g, 20 mmol), *N*-(benzyloxycarbonyloxy)succinimide (5.0 g, 20 mmol) and TEA (5 mL, 36 mmol) in $CHCl_3$ (100 mL) is stirred at r.t. for 48 h. The mixture is diluted with CH_2Cl_2 (100 mL) and extracted with 1 M aq. NaOH (3 x 50 mL). The aq. phase is extracted with Et_2O (2 x 50 mL), acidified (pH 2) with 6N aq. HCl and extracted with CH_2Cl_2 (4 x 50 mL). The combined CH_2Cl_2 extracts are dried (Na_2SO_4), filtered and evaporated to provide the title compound.

A7.2. 4-(Benzyl-methyl-carbamoyl)-4-phenyl-piperidine-1-carboxylic acid benzyl ester.

A mixture of 4-phenyl-piperidine-1,4-dicarboxylic acid monobenzyl ester (3.39 g, 10 mmol) and $SOCl_2$ (7 mL, 100 mmol) in $CHCl_3$ (150 mL) is heated at reflux for 3 h. The solvent and excess $SOCl_2$ are evaporated into a cold trap and the residue is redissolved in $CHCl_3$ (50 mL). The solution is added to a solution of

methylbenzylamine (1.45 g, 12 mmol) and DIPEA (2 mL, 12 mmol) in cold (0°C) $CHCl_3$ (100 mL). The mixture is stirred for 15 h at r.t. and then quenched with sat. aq. Na_2CO_3 (50 mL). The phases are separated and the aq. phase is extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts are washed with 1N aq. HCl (50 mL) and sat. aq. NaCl (50 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by FC (SiO_2, heptane-EtOAc) to provide the title compound.

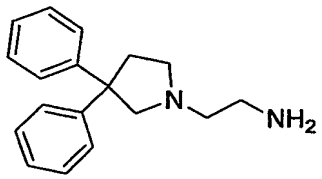
A7.3. 4-Phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide.

A mixture of 4-(benzyl-methyl-carbamoyl)-4-phenyl-piperidine-1-carboxylic acid benzyl ester (4.4 g, 10 mmol) and Pd-C (10%, 400 mg) in MeOH (200 mL) is hydrogenated at r.t. and atmospheric pressure for 3 h. The mixture is filtered and evaporated. The resiudue is purified by reversed phase MPLC to provide the title compound.

A7.4. 1-(2-Amino-ethyl)-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide.

The title compound is prepared from 4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide and (2-bromo-ethyl)-carbamic acid tert-butyl ester (Example A2.3) using the methods for the preparation of Example A2.4 and Example A2.5.

A8. 2-(3,3-Diphenyl-pyrrolidin-1-yl)-ethylamine.



A8.1. 3,3-Diphenyl-pyrrolidine.

A suspension of $LiAlH_4$ (560 mg, 14.75 mmol) in THF (50 mL) is cooled at 0°C and a solution of 4-bromo-2,2-diphenylbutyronitrile (1.50 g, 5 mmol) in THF (20 mL) is slowly added. The mixture is stirred at r.t. for 15 h, carefully quenched with MeOH and $NaHCO_3$ and filtered. The filtrate is evaporated, the residue taken up in CH_2Cl_2 (100 mL) and washed with sat. aq. Na_2CO_3.(50 mL). The aq. phase is re-extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic extracts are dried

(Na_2SO_4), filtered and evaporated. The residue is purified by reversed phase MPLC to provide the title compound.

A8.2. (2-Bromo-ethyl)-carbamic acid benzyl ester.

2-Bromoethylamine hydrobromide (15 g, 73 mmol) and *N*-(benzyloxycarbonyloxy)-succinimide (15.5 g, 62 mmol) are suspended in CH_2Cl_2 (150 mL) at 0°C. TEA (9 mL, 65 mmol) is added slowly keeping the temperature at 0°C. After 1h the mixture is washed with 0.5M aq. $KHSO_4$ (50 mL) and sat. aq. NaCl (50 mL), the organic phase is dried (Na_2SO_4), filtered and evaporated to provide the title compound.

A8.3. [2-(3,3-Diphenyl-pyrrolidin-1-yl)-ethyl]-carbamic acid benzyl ester.

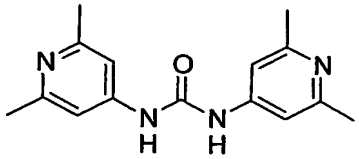
(2-Bromo-ethyl)-carbamic acid benzyl ester (1.10 g, 4.26 mmol), 3,3-diphenyl-pyrrolidine (836 mg, 3.75 mmol) and DIPEA (1.0 mL 5.7 mmol) are dissolved in THF (20 mL) and stirred for 15 h at reflux. The mixture is quenched with Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts are washed with sat. aq. Na_2CO_3 (30 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by FC (SiO_2, EtOAc-heptane) to provide the title compound.

A8.4. 2-(3,3-Diphenyl-pyrrolidin-1-yl)-ethylamine.

[2-(3,3-Diphenyl-pyrrolidin-1-yl)-ethyl]-carbamic acid benzyl ester (1.44 g, 3.6 mmol) is dissolved in MeOH (50 mL) and Pd-C (10%, 150 mg) is added. The mixture is stirred under hydrogen atmosphere for 15 h. The mixture is filtered and the filtrate evaporated to provide the title compound.

Preparation of Intermediates. Example B.

B1. 1,3-Bis-(2,6-dimethyl-pyridin-4-yl)-urea.



B1.1. 2,6-Dimethyl-4-nitro-pyridine 1-oxide.

Lutidine-*N*-oxide (19 g, 155 mmol) is cooled at 0°C and a mixture of fuming HNO_3 (100 %, 37.5 mL) and conc. H_2SO_4 (95-97%, 52.5 mL), prepared by addition of H_2SO_4 to HNO_3 at 0°C, is added slowly. The mixture is heated at 80°C for 3h. The cooled mixture is carefully poured into ice-water (500 mL). A white precipitate forms that is filtered. The precipitate is dissolved in CH_2Cl_2 (100 mL) and the filtrate is extracted with CH_2Cl_2 (4x 75 mL). The organic extracts are combined with the dissolved precipitate and washed with sat. aq. NaCl (2 x 75 mL), dried (Na_2SO_4), filtered and evaporated to provide the title compound.

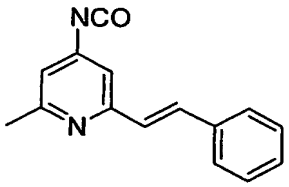
B1.2. 2,6-Dimethyl-pyridin-4-ylamine.

2,6-Dimethyl-4-nitro-pyridine 1-oxide (9.62 g, 57 mmol) is dissolved in AcOH (300 mL) and Fe (powder, 29 g) is added. The mixture is stirred for 1 h at 100°C. The mixture is cooled to r.t. and filtered. The filtercake is thoroughly washed with AcOH and then discarded. The filtrate is evaporated, diluted with water (100 mL), basified with NaOH (1 M, 100 mL), filtered from the formed precipitate and the filtrate is extracted with $CHCl_3$ (10 x 50 mL). The combined organic extracts are dried (Na_2SO_4), filtered and evaporated. The residue is crystallized from heptane-$CHCl_3$ to provide the title compound.

B1.3. 1,3-Bis-(2,6-dimethyl-pyridin-4-yl)-urea.

2,6-Dimethyl-pyridin-4-ylamine (1.22 g, 10 mmol) is dissolved in dry dioxane (30 mL) and CDI (891 mg, 5.5 mmol) is added. The mixture is heated at 80°C for 1 h. Further CDI (160 mg) is added and stirring is continued for 15 h. The mixture is evaporated and purified by FC (SiO_2, EtOAc-MeOH) to provide the title compound.

B2. 4-Isocyanato-2-methyl-6-(*E*)-styryl-pyridine.



B2.1. 2-Methyl-6-(*E*)-styryl-isonicotinic acid.

A suspension of 2-chloro-6-methyl-isonicotinic acid (171.6 mg, 1 mmol), (*E*)-2-phenyl-etheneboronic acid (180.0 mg, 1.2 mmol), K_2CO_3 (414 mg), $Pd(dppf)Cl_2$-CH_2Cl_2 (27 mg) in CH_3CN-H_2O (3:1, 10 mL) is stirred under argon at 90°C for 15 h. The solution is cooled to r.t. and aq. hydrochloric acid (2 M, 1.5 mL) is added to adjust the pH at 3. The mixture is evaporated to dryness and purified by reversed phase MPLC to provide the title compound.

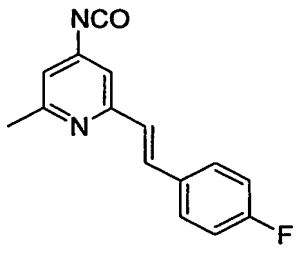
B2.2. 2-Methyl-6-(*E*)-styryl-isonicotinoyl azide.

To a solution of 2-methyl-6-(*E*)-styryl-isonicotinic acid (214 mg, 0.89 mmol) in DMF (5 mL) is added at 0°C TEA (0.21 mL, 1.5 mmol) and slowly (30 min) DPPA (366 mg, 1.33 mmol). The reaction mixture is stirred for 0.5 h at 0°C and 0.5 h at r.t. The reaction is quenched with ice (20 g) and extracted with Et_2O (6 x 30 mL). The combined organic extracts are washed successively with saturated $NaHCO_3$ (2 x 15 mL) and water (2 x 10 mL), and are evaporated in vacuo without heating. The residue is purified by FC (SiO_2, EtOAc-heptane) to provide the title compound.

B2.3. 4-Isocyanato-2-methyl-6-(*E*)-styryl-pyridine.

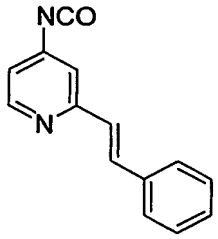
2-Methyl-6-(*E*)-styryl-isonicotinoyl azide (79.9 mg, 0.3 mmol) is dissolved in dry toluene (4 mL) and heated at reflux for 2h. The resulting solution of the title compound is carried forward without further isolation.

B3. 2-[(*E*)-2-(4-Fluoro-phenyl)-vinyl]-4-isocyanato-6-methyl-pyridine.



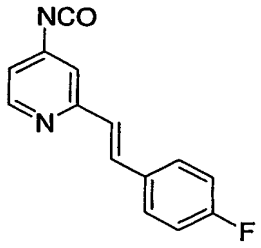
The title compound is prepared from (*E*)-2-(4-fluoro-phenyl)-etheneboronic acid and 2-chloro-6-methyl-isonicotinic acid using the method described in Example B2.

B3. 4-Isocyanato-2-(*E*)-styryl-pyridine.



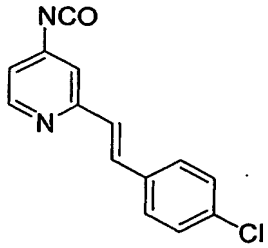
The title compound is prepared from (*E*)-2-phenyl-etheneboronic acid and 2-chloro-isonicotinic acid using the method described in Example B2.

B5. 2-[(*E*)-2-(4-Fluoro-phenyl)-vinyl]-4-isocyanato-pyridine.



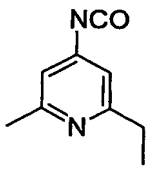
The title compound is prepared from (*E*)-2-(4-fluoro-phenyl)-etheneboronic acid and 2-chloro-isonicotinic acid using the method described in Example B2.

B6. 2-[(*E*)-2-(4-Chloro-phenyl)-vinyl]-4-isocyanato-pyridine.



The title compound is prepared from (*E*)-2-(4-chloro-phenyl)-etheneboronic acid and 2-chloro-isonicotinic acid using the method described in Example B2.

B7. 2-Ethyl-4-isocyanato-6-methyl-pyridine.



B7.1. 2-Chloro-6-methyl-isonicotinic acid tert-butyl ester.

N,N-dimethylformamide-di-*tert.*-butyl-acetal (19 mL, 80 mmol) is added during 40 min to a hot (65°C, flask temperature) suspension of 2-chloro-6-methyl-isonicotinic acid (3.40 g, 19.8 mmol) in dry toluene (100 mL). The clear orange solution is stirred at 80°C for 48 h, cooled to r.t. and diluted with toluene (100 mL). The solution is washed with water (2 x 40 mL), sat. aq. $NaHCO_3$ (3 x 30 mL) and sat. aq. NaCl (25 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by FC (SiO_2, CH_2Cl_2-MeOH) to provide the title compound.

B7.2. 2-Ethyl-6-methyl-isonicotinic acid.

A solution of ethylmagnesiumbromide (freshly prepared from ethylbromide (392 mg, 3.6 mmol) and magnesium (83 mg, 3.4 mmol)) in Et_2O (10 mL) is added to a cooled (-40°C) and mechanically stirred solution of 2-chloro-6-methyl-isonicotinic acid tert-butyl ester (0.76 g, 3.34 mmol), $Fe(acac)_3$ (21.2 mg, 0.06 mmol) and NMP (0.6 mL) in THF (60 mL). The mixture is warmed to r.t. during 0.5 h, diluted with Et_2O (150 mL) and quenched with aq. $KHSO_4$ (1 M, 40 mL). The phases are separated and the aq. phase is extracted with Et_2O (2 x 50 mL). The combined organic extracts are dried ($MgSO_4$), filtered and evaporated. The residue is purified by reversed phase MPLC. The obtained 2-ethyl-6-methyl-isonicotinic acid tert-butyl ester is dissolved in CH_2Cl_2 (10 mL). TFA (10 mL) is added and the mixture stirred at r.t. for 0.5 h. The mixture is evaporated and the residue dried in HV to provide the title compound.

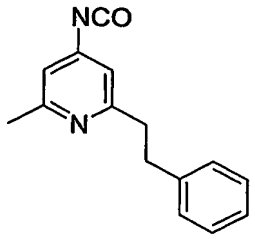
B7.3. 2-Ethyl-6-methyl-isonicotinoyl azide.

The title compound is prepared from 2-ethyl-6-methyl-isonicotinic acid using the method described in Example B2.2.

B7.4. 2-Ethyl-4-isocyanato-6-methyl-pyridine.

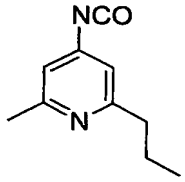
The title compound is prepared from 2-ethyl-6-methyl-isonicotinoyl azide using the method described in Example B2.3.

B8. 4-Isocyanato-2-methyl-6-phenethyl-pyridine.



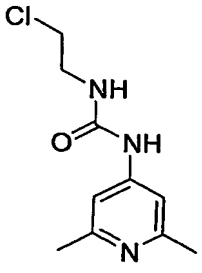
The title compound is prepared from 2-chloro-6-methyl-isonicotinic acid tert-butyl ester (Example B7.1) and phenethylbromide using the method described in Example B7.

B9. 4-Isocyanato-2-methyl-6-propyl-pyridine.



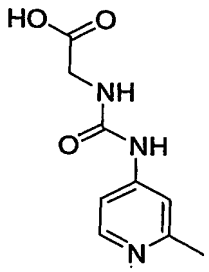
The title compound is prepared from 2-chloro-6-methyl-isonicotinic acid tert-butyl ester (Example B7.1) and propylbromide using the method described in Example B7.

B10. 1-(2-Chloro-ethyl)-3-(2,6-dimethyl-pyridin-4-yl)-urea.



2,6-Dimethyl-pyridin-4-ylamine (Example 1.2, 1.22 g, 10 mmol) is dissolved in dry THF (30 mL) and 1-chloro-2-isocyanato-ethane (1.06 g, 10 mmol) is added. The mixture is stirred at r.t. for 15 h. The mixture is evaporated and the residue purified by reversed phase MPLC to provide the title compound.

B11. [3-(2-Methyl-pyridin-4-yl)-ureido]-acetic acid.



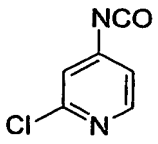
B10.1. 2-Methyl-pyridin-4-ylamine.

The material is prepared from commercially available 2-methyl-4-nitro-pyridine 1-oxide using the method described for Example 1.2.

B10.2 [3-(2-Methyl-pyridin-4-yl)-ureido]-acetic acid.

2-Methyl-pyridin-4-ylamine (1.08 g, 10 mmol) is dissolved in dry THF (30 mL) and isocyanatoacetic acid ethyl ester (1.29 g, 10 mmol) is added. The mixture is stirred at r.t. for 15 h. The mixture is evaporated and 6N aq. HCl (20 mL) is added. The mixture is stirred at 50°C for 6 h, evaporated and the residue purified by reversed phase MPLC to provide the title compound.

B12. 2-Chloro-4-isocyanatopyridine.

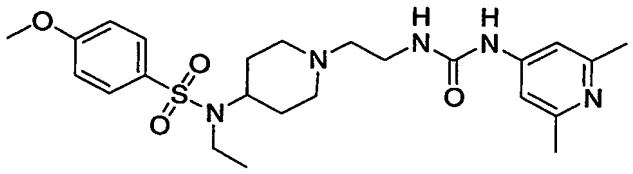


The title compound is prepared from commercially available 2-chloro-isonicotinic acid using the method described in Example B2.3.

PREPARATION OF FINAL PRODUCTS

Example 1.

N-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-benzenesulfonamide.



A suspension of *N*-[1-(2-amino-ethyl)-piperidin-4-yl]-*N*-ethyl-4-methoxy-benzene-sulfonamide (Example A2, 85 mg, 0.25 mmol), TEA (35 μL, 0.25 mmol) and 1,3-bis-(2,6-dimethyl-pyridin-4-yl)-urea (Example B1, 67.5 mg 0.25 mmol) in dioxane (2 mL) is heated at reflux for 24h. The solvent is evaporated and the residue purified by HPLC to provide the title compound.

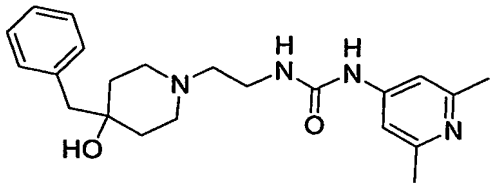
The following examples are pepared from Examples A1-A8 and Example B1 using the method described for Example 1.

Example No	Example	t_R	$[M+H]^+$
1	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-benzenesulfonamide	0.65	490.22
2	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-fluoro-benzenesulfonamide	0.65	478.26
3	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-*N*-propyl-benzenesulfonamide	0.68	504.27
4	*N* -(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-*N* -propyl-benzenesulfonamide	0.68	492.23

5	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea	0.63	367.42
6	1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.70	500.47
7	1-(2,6-Dimethyl-pyridin-4-yl)-3-[2-(3,3-diphenyl-pyrrolidin-1-yl)-ethyl]-urea	0.68	415.20

Example 8.

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea.

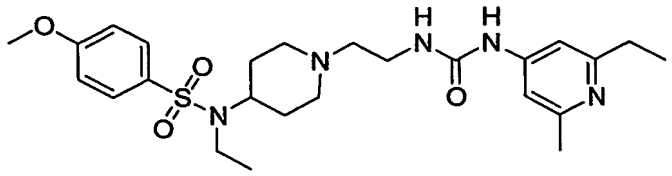


A suspension of commercially available 4-benzyl-piperidin-4-ol (385 mg, 2.0 mmol), $NaHCO_3$ (672 mg, 8.0 mmol) and 1-(2-chloro-ethyl)-3-(2,6-dimethyl-pyridin-4-yl)-urea (Example B10, 227.7 mg 1.0 mmol) in THF (4 mL) is stirred at r.t. for 4 days. The mixture is quenched with Na_2CO_3 (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts are washed with sat. aq. Na_2CO_3 (10 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by HPLC to provide the title compound.

Example No	Example	t_R	$[M+H]^+$
8	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea	0.58	383.14

Example 9.

***N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-benzenesulfonamide.**



To a solution of *N*-[1-(2-amino-ethyl)-piperidin-4-yl]-*N*-ethyl-4-methoxy-benzenesulfonamide (Example A2, 85 mg, 0.25 mmol) in CH_2Cl_2 is added a freshly prepared solution of 2-ethyl-4-isocyanato-6-methyl-pyridine (Example B7, 0.3 mmol) in toluene (2 mL). The mixture is stirred for 15 h at 20 °C. Evaporation of the solvent and purification by HPLC provides the title compound.

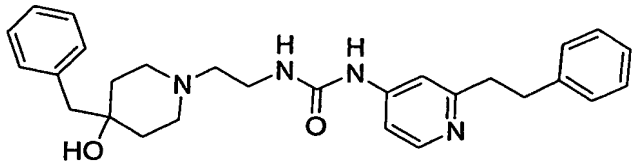
The following examples are pepared from Examples A1-A7 and Examples B2-B9 using the method described for Example 9.

Example No	Example	t_R	$[M+H]^+$
9	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-benzenesulfonamide	0.67	504.25
10	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-ethyl-6-methyl-pyridin-4-yl)-urea	0.66	381.27
11	1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.72	514.34
12	*N*-Ethyl-4-methoxy-*N*-(1-{2-[3-(2-methyl-6-propyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide	0.69	518.29
13	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-6-propyl-pyridin-4-yl)-urea	0.70	395.55

14	1-{2-[3-(2-Methyl-6-propyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.74	528.50
15	*N*-Ethyl-4-methoxy-*N*-(1-{2-[3-(2-methyl-6-phenethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide	0.74	580.45
16	1-(2-{3-[2-Methyl-6-((*E*)-styryl)-pyridin-4-yl]-ureido}-ethyl)-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.79	588.46
17	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-fluoro-phenyl)-vinyl]-6-methyl-pyridin-4-yl}-urea	0.76	473.42
18	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-((*E*)-styryl)-pyridin-4-yl]-urea	0.67	457.40
19	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-fluoro-phenyl)-vinyl]-pyridin-4-yl}-urea	0.69	475.40
20	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-chloro-phenyl)-vinyl]-pyridin-4-yl}-urea	0.71	491.38

Example 21.

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-phenethyl-pyridin-4-yl)-urea.



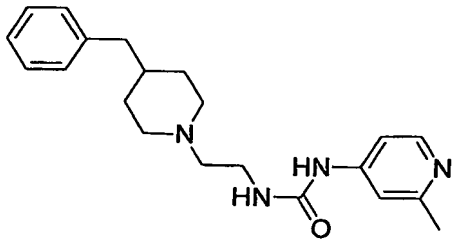
A suspension of 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-((*E*)-styryl)-pyridin-4-yl]-urea (Example 18, 47.0 mg, 0.1 mmol) and Pd-C (10 %, 10 mg) in MeOH (10 mL) is stirred under hydrogen atmosphere for 15 h. The catalyst is filtered off and the reaction mixture evaporated to provide the title compound.

The following compounds are prepared from Examples 16-19 using the method described for Example 21.

Example No	Example	t_R	$[M+H]^+$
21	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-phenethyl-pyridin-4-yl)-urea	0.67	459.41
22	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[2-(4-fluoro-phenyl)-ethyl]-pyridin-4-yl}-urea	0.68	477.44
23	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-{2-[2-(4-fluoro-phenyl)-ethyl]-6-methyl-pyridin-4-yl}-urea	0.75	475.49
24	1-{2-[3-(2-Methyl-6-phenethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.79	590.53

Example 25.

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-pyridin-4-yl)-urea.



Example 25.1.

1-[2-(4-Benzyl-piperidin-1-yl)-2-oxo-ethyl]-3-(2-methyl-pyridin-4-yl)-urea.

To a cooled (0°C) mixture of [3-(2-methyl-pyridin-4-yl)-ureido]-acetic acid (Example 11, 105 mg, 0.5 mmol), commercially available 4-benzylpiperidine (105 mg, 0.6 mmol), HOBt (81 mg, 0.6 mmol), TEA (0.14 mL, 1 mmol) and a cat. amount of DMAP in CH_2Cl_2 (20 mL) is added EDC (115 mg, 0.6 mmol). The mixture is stirred at r.t. for 15 h. The mixture is quenched with sat. aq. Na_2CO_3 (25 mL), the phases are separated, and the aq. phase is extracted with CH_2Cl_2 (3 x 30

mL). The combined organic extracts are dried (Na_2SO_4), filtered and evaporated to provide the crude title compound.

Example 25.2.

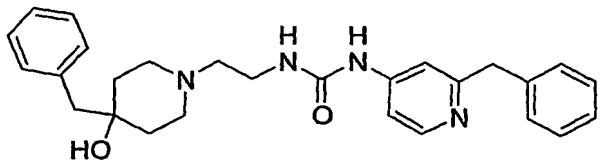
1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-pyridin-4-yl)-urea.

The crude 1-[2-(4-benzyl-piperidin-1-yl)-2-oxo-ethyl]-3-(2-methyl-pyridin-4-yl)-urea (Example 25.1, 0.5 mmol) is dissolved in THF (5 mL) and added to a cooled (0°C) suspension of $LiAlH_4$ (100 mg, 2.5 mmol) in THF (20 mL). The mixture is warmed during 15 h to r.t. The reaction mixture is carefully added to EtOAc (100 mL) and MeOH (5 mL), and, subsequently, sat. aq. $NaHCO_3$ (2 mL) are added. The mixture is filtered, the filtercake washed with MeOH (2 x 50 mL), and the filtrate is evaporated. The residue is taken up in a minimal amount of MeOH, diluted with CH_2Cl_2, dried (Na_2SO_4), filtered and evaporated. The residue is purified by HPLC to provide the title compound.

Example No	Example	t_R	$[M+H]^+$
25	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-pyridin-4-yl)-urea	0.62	353.12

Example 26.

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-benzyl-pyridin-4-yl)-urea.



Example 26.1.

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-chloro-pyridin-4-yl)-urea.

The title compound is prepared from 1-(2-amino-ethyl)-4-benzyl-piperidin-4-ol (Example A6) and 2-chloro-4-isocyanatopyridine (Example B12) using the method described in Example 9.

Example 26.2.

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-benzyl-pyridin-4-yl)-urea.

A mixture of 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-chloro-pyridin-4-yl)-urea (98 mg, 0.3 mmol), *B*-benzyl-9-BBN (0.5 M in THF, 4 mL, 2 mmol), triphenylphosphine (29 mg, 0.11 mmol), tetrakis(triphenylphosphine)palladium(0) (11 mg, 0.01 mmol), 2 M aq. K_2CO_3 (0.5 mL) and dimethoxyethane (1 mL) is degassed and heated under argon at 90°C for 7 days. The mixture is evaporated and the residue purified by preparative HPLC to provide the title compound.

Example No	Example	t_R	$[M+H]^+$
26	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-benzyl-pyridin-4-yl)-urea	0.65	445.40

EXAMPLE 27. IN VITRO BIOLOGICAL CHARACTERIZATION

The inhibitory activity of the compounds of General Formula 1 on the actions of urotensin II can be demonstrated using the test procedures described hereinafter:

1) INHIBITION OF HUMAN [^{125}I]-UROTENSIN II BINDING TO A RHABDOMYOSARCOMA CELL LINE

Whole cell binding of human [^{125}I]-urotensin II is performed using human-derived TE-671 rhabdomyosarcoma cells (Deutsche Sammlung von Mikroorganismen und Zellkulturen, cell line #ACC-263), by methods adapted from a whole cell endothelin binding assay (Breu V et al, In vitro characterization of Ro-46-2005, a novel synthetic non-peptide antagonist of ET_A and ET_B receptors. FEBS Lett. 1993, 334, 210-214).

The assay is performed in 250 µL Dulbecco's Modified Eagle Medium, pH 7.4 (GIBCO BRL, CatNo 31885-023), including 25 mM HEPES (Fluka, CatNo 05473), 1.0 % DMSO (Fluka, CatNo 41644) and 0.5% (w/v) BSA Fraction V (Fluka, CatNo 05473) in polypropylene microtiter plates (Nunc, CatNo 442587). 300'000 suspended cells are incubated with gentle shaking for 4 h at 20°C with 20 pM

human [^{125}I]Urotensin II (Anawa Trading SA, Wangen, Switzerland, 2130Ci/mmol) and increasing concentrations of unlabeled antagonist. Minimum and maximum binding are derived from samples with and without 100 nM unlabelled U-II, respectively. After the 4 h incubation period, the cells are filtered onto GF/C filterplates (Packard, CatNo 6005174). The filter plates are dried, and then 50 µL scintillation cocktail (Packard, MicroScint 20, CatNo 6013621) is added to each well. The filterplates are counted in a microplate counter (Packard Bioscience, TopCount NXT).

All test compounds are dissolved and diluted in 100% DMSO. A ten-fold dilution into assay buffer is performed prior to addition to the assay. The final concentration of DMSO in the assay is 1.0%, which is found not to interfere with the binding. IC50 values are defined as the concentration of antagonist inhibiting 50% of the specific binding of [^{125}I]human U-II. Specific binding is the difference between maximum binding and minimum binding, as described above. An IC_{50} value of 0.206 nM is found for unlabeled human U-II. The compounds of the invention are found to have IC_{50} values ranging from 0.1 to 1000 nM in this assay.

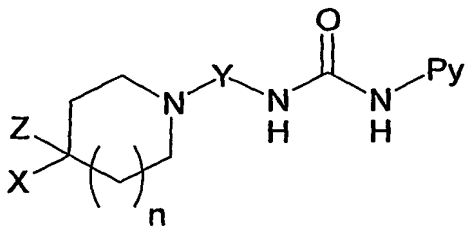
2) INHIBITION OF HUMAN UROTENSIN II-INDUCED CONTRACTIONS ON ISOLATED RAT THORACIC AORTA :

Adult male rats (Wistar or Sprague-Dawley) are euthanized by CO_2. An aortic segment (12mm) is isolated immediately distal to the left sub-clavian arterial branch, and vessel rings (3mm wide) are prepared. The endothelium is removed by inserting the tip of a watchmaker's forceps inside the lumen and gently rolling the tissue on a moist filter paper. Aortic rings are suspended in tissue baths (10 mL) containing Krebs-Henseleit buffer of the following composition (mM): NaCl 115; KCl 4.7; $MgSO_4$ 1.2; KH_2PO_4 1.5; $CaCl_2$ 2.5; $NaHCO_3$ 25; glucose 10. Bathing solution is maintained at 37°C and aerated with 95%O_2/ 5%CO_2 (pH 7.4). A resting force of 2 g (19.6 mN) is applied to the vessel, and changes in force generation are recorded using an EMKA automated system (EMKA Technologies SA, Paris, France). The viability of each aortic ring is determined by contraction to a depolarising concentration of KCl (60 mM). After washout, the successful removal of endothelium is tested by the failure of acetylcholine (10 µM) to relax

vessels constricted with phenylephrine (1 μM). Following further washout, tissues are exposed to either drug vehicle (control) or test compound for 20 minutes. A cumulative concentration-response curve to h-UII (30 pM-0.3 μM) is then obtained. Contraction of vessels to h-UII is expressed as a percentage of the initial contraction to KCl (60 mM). If the test compound displays competitive antagonism (causes parallel right-ward displacement of concentration-effect curve without diminishing the maximum response), then the inhibitory potency is quantified by calculation of the pA_2 value for the test compound (pA_2 value is the negative logarithm of the theoretical antagonist concentration which induces a two-fold shift in the EC_{50} value for h-U-II).

CLAIMS

1. Compounds of the General Formula 1.



General Formula 1

wherein:

Py represents pyridin-4-yl which is disubstituted in positions 2 and 6, whereby the substituent in position 2 is lower alkyl, aryl-lower alkyl, or (*E*)-2-aryl-ethen-1-yl, and the substituent in position 6 is hydrogen or lower alkyl;

X represents aryl; aryl-O-; aryl-lower alkyl-; R^1-SO_2NR^2-; R^1-$CONR^2$-; R^1-NR^3CONR^2-; R^1-NR^2CO-; or X and Z represent together with the carbon atom to which they are attached an exocyclic double bond which bears an aryl substituent at the thus formed methylene group;

Y represents $-C(R^4)(R^5)(CH_2)_m-$ or $-(CH_2)_mC(R^4)(R^5)-$;

Z represents hydrogen; in case X represents aryl or aryl-lower alkyl Z represents hydrogen, hydroxyl, carboxyl, R^1-NR^2CO-; or in case X represents aryl or aryl-lower alkyl and n represents the number 0, Z represents hydrogen, hydroxyl, carboxyl, R^1-NR^2CO-, aryl, aryl-lower alkyl;

n represents the numbers 0 or 1;

m represents the numbers 1 or 2;

R^1 represents aryl; lower alkyl; aryl-lower alkyl; or a saturated carbocyclic ring;

R^2 and R^3 represent independently hydrogen; lower alkyl; aryl-lower alkyl; or a saturated carbocyclic ring;

R^4 represents hydrogen; lower alkyl; aryl; aryl-lower alkyl; or forms together with R^5 a saturated carbocyclic ring including the carbon atom to which R^4 and R^5 are attached as ring atom;

R^5 represents hydrogen; methyl; or forms together with R^4 a saturated carbocyclic ring including the carbon atom to which R^4 and R^5 are attached as ring atom;

and configurational isomers, optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates; as well as their pharmaceutically acceptable salts, solvent complexes, and morphological forms.

2. Compounds of General Formula 1 in claim 1, wherein m represents 1 and Py, R^4, R^5, X, Z, and n have the meaning given in General Formula 1.

3. Compounds of General Formula 1 in claim 1, wherein Py represents pyridin-4-yl disubstituted in position 2 and 6 with lower-alkyl, and X, Y, Z, and n have the meaning given in General Formula 1.

4. Compounds of General Formula 1 in claim 1, wherein Py represents pyridin-4-yl disubstituted in position 2 with aryl-lower alkyl and in position 6 with lower-alkyl, and X, Y, Z, and n have the meaning given in General Formula 1.

5. Compounds of General Formula 1 in claim 1, wherein R^4 and R^5 represent independently hydrogen or methyl, and Py, X, Z, n, and m have the meaning given in General Formula 1.

6. Compounds of General Formula 1 in claim 1, wherein X represents aryl or aryl-lower alkyl, Z represents HO-, n represents 1, and Py, and Y have the meaning given in General Formula 1.

7. Compounds of General Formula 1 in claim 1, wherein X represents aryl or aryl-lower alkyl, Z represents hydrogen, n represents 1, and Py, and Y have the meaning given in General Formula 1.

8. Compounds of General Formula 1 in claim 1, wherein X and Z independently represent aryl, n represents 0, and Py, and Y have the meaning given in General Formula 1

9. Compounds of General Formula 1 in claim 1, wherein X represents R^1-SO_2NR^2-, R^1-$CONR^2$-, R^1-NR^2CONR^3-; Z represents hydrogen, and R^1, R^2, R^3, Py, and Y have the meaning given in General Formula 1.

10. Compounds of General Formula 1 in claim 1, wherein X represents R^1-NR^2CO-; Z represents aryl or hydrogen, and R^1, R^2, Py, and Y have the meaning given in General Formula 1.

11. Compounds of General Formula 1 in claim 1, wherein m represents 1, Py represents pyridin-4-yl disubstituted in position 2 and 6 with lower-alkyl, and X, R^4, R^5, Z, and n have the meaning given in General Formula 1.

12. Compounds of General Formula 1 in claim 1, wherein m represents 1, Py represents pyridin-4-yl disubstituted in position 2 with aryl-lower alkyl and in position 6 with lower-alkyl, and X, R^4, R^5, Z, and n have the meaning given in General Formula 1.

13. Compounds of General Formula 1 in claim 1, wherein m represents 1, R^4 and R^5 represent hydrogen, and Py, X, Z, and n have the meaning given in General Formula 1.

14. Compounds of General Formula 1 in claim 1, wherein m represents 1, X represents aryl or aryl-lower alkyl, Z represents HO-, n represents 1, and Py, R^4, and R^5 have the meaning given in General Formula 1.

15. Compounds of General Formula 1 in claim 1, wherein m represents 1, X represents aryl or aryl-lower alkyl, Z represents hydrogen, n represents 1, and Py, R^4, and R^5 have the meaning given in General Formula 1.

16. Compounds of General Formula 1 in claim 1, wherein m represents 1, X represents R^1-SO_2NR^2-, R^1-$CONR^2$-, R^1-NR^2CONR^3-; Z represents hydrogen,

and n, Py, R^1, R^2, R^3, R^4, and R^5 have the meaning given in General Formula 1.

17. Compounds of General Formula 1 in claim 1, wherein m represents 1, X represents R^1-NR^2CO-; Z represents aryl or hydrogen, n represents 1, and Py, R^1, R^2, R^4, and R^5 have the meaning given in General Formula 1.

18. Compounds of General Formula 1 in claim 1, wherein m represents 1, R^4 and R^5 represent hydrogen, Py represents pyridin-4-yl disubstituted in position 2 with methyl and in position 6 with lower-alkyl, and X, Z, and n have the meaning given in General Formula 1.

19. Compounds of General Formula 1 in claim 1, wherein m represents 1, R^4 and R^5 represent hydrogen, X represents aryl or aryl-lower alkyl, Z represents HO-, n represents 1, and Py has the meaning given in General Formula 1.

20. Compounds of General Formula 1 in claim 1, wherein m represents 1, R^4 and R^5 represent hydrogen, X represents aryl or aryl-lower alkyl, Z represents hydrogen, n represents 1, and Py has the meaning given in General Formula 1.

21. Compounds of General Formula 1 in claim 1, wherein m represents 1, R^4 and R^5 represent hydrogen, X represents aryl-SO_2NR^2-, Z represents hydrogen, and R^2, n and Py have the meaning given in General Formula 1.

22. Compounds of General Formula 1 in claim 1, wherein m represents 1, R^4 and R^5 represent hydrogen, X represents aryl-NR^2CO- or aryl-lower alkyl-NR^2CO-, Z represents aryl or hydrogen, n represents 1, and Py and R^2 have the meaning given in General Formula 1.

23. The compound according to any one of claims 1 to 22 that is selected from the group consisting of

N-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-benzenesulfonamide;

N-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-fluoro-benzenesulfonamide;

N-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-*N*-propyl-benzenesulfonamide;

N-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-*N*-propyl-benzenesulfonamide;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea;

1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide;

1-(2,6-Dimethyl-pyridin-4-yl)-3-[2-(3,3-diphenyl-pyrrolidin-1-yl)-ethyl]-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea;

N-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-benzenesulfonamide;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-ethyl-6-methyl-pyridin-4-yl)-urea;

1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide;

N-Ethyl-4-methoxy-*N*-(1-{2-[3-(2-methyl-6-propyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-6-propyl-pyridin-4-yl)-urea;

1-{2-[3-(2-Methyl-6-propyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide;

N-Ethyl-4-methoxy-*N*-(1-{2-[3-(2-methyl-6-phenethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide;

1-(2-{3-[2-Methyl-6-((*E*)-styryl)-pyridin-4-yl]-ureido}-ethyl)-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-fluoro-phenyl)-vinyl]-6-methyl-pyridin-4-yl}-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-((*E*)-styryl)-pyridin-4-yl]-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-fluoro-phenyl)-vinyl]-pyridin-4-yl}-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-chloro-phenyl)-vinyl]-pyridin-4-yl}-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-phenethyl-pyridin-4-yl)-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[2-(4-fluoro-phenyl)-ethyl]-pyridin-4-yl}-urea;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-{2-[2-(4-fluoro-phenyl)-ethyl]-6-methyl-pyridin-4-yl}-urea;

1-{2-[3-(2-Methyl-6-phenethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide;

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-pyridin-4-yl)-urea;

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-benzyl-pyridin-4-yl)-urea.

24. Pharmaceutical compositions containing a compound of any one of claims 1 to 23 and usual carrier materials and adjuvants for the treatment of disorders which are associated with a dysregulation of urotensin II or urotensin II receptors, or disorders associated with vascular or myocardial dysfunction, comprising hypertension, atherosclerosis, angina or myocardial ischemia, congestive heart failure, cardiac insufficiency, cardiac arrhythmias, renal ischemia, chronic kidney disease, renal failure, stroke, cerebral vasospasm, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, diabetes, diabetic arteriopathy, diabetic nephropathy, connective tissue diseases, cirrhosis, asthma, chronic obstructive pulmonary disease, high-altitude

pulmonary edema, Raynaud's syndrome, portal hypertension, thyroid dysfunction, pulmonary edema, pulmonary hypertension, or pulmonary fibrosis.

25. Pharmaceutical compositions containing a compound of any one of claims 1 to 23 and usual carrier materials and adjuvants for the treatment of disorders comprising restenosis after balloon or stent angioplasty, for treatment of cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, sickle cell acute chest syndrome, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, addictions, schizophrenia, Alzheimer's disease, anxiety, obsessive-compulsive behavior, epileptic seizures, stress, depression, dementias, neuromuscular disorders, or neurodegenerative diseases.

26. The use of one or more compounds of any one of claims 1 to 23 in combination with other pharmacologically active compounds for the treatment of hypertension, atherosclerosis, angina or myocardial ischemia, congestive heart failure, cardiac insufficiency, cardiac arrhythmias, renal ischemia, chronic kidney disease, renal failure, stroke, cerebral vasospasm, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, diabetes, diabetic arteriopathy, diabetic nephropathy, connective tissue diseases, cirrhosis, asthma, chronic obstructive pulmonary disease, high-altitude pulmonary edema, Raynaud's syndrome, portal hypertension, thyroid dysfunction, pulmonary edema, pulmonary hypertension, or pulmonary fibrosis, restenosis after balloon or stent angioplasty, cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, sickle cell acute chest syndrome, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, addiction, schizophrenia, Alzheimer's disease, anxiety, obsessive-compulsive behavior, epileptic seizures, stress, depression, dementias, neuromuscular disorders, or neurodegenerative diseases.

27. The use of one or more compounds of any one of claims 1 to 23 in combination with other pharmacologically active compounds comprising ACE inhibitors, angiotensin II receptor antagonists, endothelin receptor antagonists, vasopressin antagonists, beta-adrenergic antagonists, alpha-adrenergic antagonists, vasopressin antagonists, TNFalpha antagonists, or peroxisome proliferator activator receptor modulators.

28. The method of treating a patient suffering from a disorder given in any one of claims 24 to 27 by administering a pharmaceutical composition according to any one of claims 24 and 25.

Abstract

The invention relates to novel pyridine derivatives and related compounds and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as neurohormonal antagonists.